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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,044	02/26/97	BYWATER M	1614-178P

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/776,044	Applicant(s) Bywater et al.
	Examiner Yvonne Eyler	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-12 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-12 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3.5

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-12 are pending and under consideration in the application.

Claim Objections

1. Claim 10 is objected to because of the following informalities: Claim 10 recites "The method of any of..." but depends only from claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. Claim 12 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

The recitation of determining sequence or sequences of the p53 gene in claim 11 appears to limit the method of determination of mutations to determination of mutations in p53. Therefore, claim 12 is not further limiting of claim 11.

3. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "determining from the presence, nature and location of any such mutation or mutations the influence thereof on the biological function of the corresponding protein and thereby on the properties of the neoplasia" is vague and indefinite. While the determination of the presence or absence of a mutation is clear, the determination of the "nature" and the

determination of the "location" is not. It is not clear what is meant to be encompassed by the "nature" of the mutation. It is not clear if this is to indicate changes such as insertions, deletions, or substitutions; if this is to indicate transversions or other specific types of chemical changes; if this is to indicate general conservative versus non-conservative changes; or if this is to indicate some other "nature" of change or mutation. Without a precise definition of the "nature" of the mutation either within the specification or the claim language, one of skill in the art could not determine if a mutation possessed the instantly encompassed "nature" or not. Likewise, it cannot be determined what is to be encompassed by the "location" of the mutation. It is not clear if this is limited to, for example, mutations within promotor regions versus encoding regions, within conserved regions versus non-conserved regions, within specified domains of the protein, within specified codons of the gene, or some other "location." Again, absent a precise definition of what "determination of location" is meant to encompass, either within the specification or the claims, one of skill could not determine if a detected mutation met the instantly claimed invention.

The claim also recites determining the "influence" of the mutation on the "biological function" of the protein. The metes and bounds of the activities and consequences encompassed by the term "influence" cannot be determined and there is no clarifying definition provided. Additionally, the metes and bounds of the activities which are encompassed by the term "biological function" cannot be determined and no clarifying definition is provided. Thus, one of skill could not determine if a mutation met the claim requirements or not, since it is unclear what parameters to measure. Similarly, the claim recites that determination of presence, nature,

location, influence all thereby correspond to and facilitate determination of the "properties" of the neoplasia. Again, there is no precise, clarifying definition of the metes and bounds of what is encompassed within the "properties" of the neoplasia and thus, again, one of skill in the art would not be able to determine if a given mutation met the claim language since it is not clear what is to be measured, detected, or determined about the neoplasia. Claim 2 recites that the "properties" **include** aggressiveness and metastatic potential but provide no information regarding what else the "properties" include and thus is not found to be clarifying.

Finally, claim 1 recites that determination of the mutation as detailed above provides guidance for "adequate" treatment of the patient. It is not clear what encompasses "adequate" treatment. What is the endpoint of adequate?

Claim 3 further recites that the analysis include part of at least one "biologically functional domain." As detailed supra, since there is no clear definition of what is encompassed as biological function, it is also unclear what is encompassed and included as a "biologically functional domain." It is not clear what part of the protein, and what activities define functionality.

Claims 4-10 do not clarify the stated deficiencies above.

Claim 10 further recites the step of "processing of the cancer-related gene including sequencing." This recited step is vague and indefinite because it is not clear what other reactions, actions, etc. are included in the "processing" in addition to sequencing.

Similarly, claim 11 is vague and indefinite in the recitation of "preferably" by solid phase based techniques, because it is not clear what other techniques are included and may be used.

Dependent claim 12 is not further clarifying.

4. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for the invention as broadly claimed. The specification is not enabling for the determination of prognosis and selection of adequate treatment of cancer based on the determination of **any** nature of a mutation in p53 or on the determination of **any** location of a mutation in p53. The specification is also not enabling for the determination of prognosis and selection of treatment based on the determination of mutations within any biologically functional domain or within any part of the p53 gene.

The specification discloses that the prognosis and responsiveness of breast cancer to post-surgical, adjunctive therapy is correlated and predictable by a combination of the presence or absence of mutations in p53 and the presence or absence of nodal involvement. The specification teaches that breast cancer may be categorized into 4 predictive groups based on the status of these two parameters. The groups are node (-), p53 mutation (-); node (-), p53 mutation (+); node (+), p53 mutation (+); and node (+), p53 mutation (-). Of these groups, the progression of all but one are taught to be relatively unaffected by adjunctive therapy. The node (-), p53 (+) is shown to respond well to adjunctive therapy. Of the p53 mutation positive groups, mutations

within conserved regions II and V are taught to be more serious with regard to prognosis than mutations within conserved regions III and IV. (pages 8-9) No information regarding any other location, domain, or part and prognosis is provided.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The instant specification enables the determination of prognosis and the prediction of responsiveness to adjunctive, post-surgical therapy of breast cancer based on the determination of the combination of node status and p53 mutation, i.e. a negative node status and p53 mutation being indicative of a likely positive response to adjunctive therapy and the presence of p53 mutations serving as a general negative prognostic factor. The specification further enables the determination of prognosis based on the conservative region in which the mutation is detected, i.e. the prognosis would be worse if the mutation were detected in conserved regions II or V. However, there is insufficient objective evidence and guidance to enable the predictable determination of prognosis or responsiveness to therapy of breast cancer based on the determination of any nature of mutation in p53, any location of p53 mutation and any p53 mutations within undefined domains, regions, and parts of the gene. There is insufficient guidance regarding the determination of the "nature" of the mutation and there is insufficient objective

evidence to render it predictable that various different natures of mutation are correlative with different prognoses and responsiveness. One of skill in the art would not be enabled by the instant specification, absent undue experimentation, to predict the effect of a transversion, for example, on prognosis of breast cancer. There is also insufficient guidance regarding the correlation between the detection of any location and prediction of prognosis. The specification teaches predictable differences between mutations within conserved regions but provides insufficient objective evidence with regard to differences, for example, between individual bases and codons, exons and introns, and specific domains as is currently encompassed by the claim language. It would require undue experimentation for one of skill in the art to predict differences in prognosis and responsiveness based on the determination of any location change. Similarly, the specification provides insufficient guidance and objective evidence regarding predictable correlations between mutations within specific defined domains of the p53 gene (the DNA binding domain or transcriptional activation domain) or indeed, with regard to the location of specific domains based on undefined biological functions. The general presence or absence of mutation is shown to have correlative value, but there is insufficient guidance and objective evidence correlating the presence of a mutation within a "domain" or any specific "part" of the p53 gene and it's affect on any undefined biological function, and the reliable predictiveness of that information on prognosis and responsiveness.

Therefore, for the reasons detailed above, it would require undue experimentation by one of skill in the art to practice the instant invention, as broadly claimed.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997).

Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) teach the detection of mutations in p53 in neoplastic samples of breast cancer as a generally poor prognostic or diagnostic factor and as prognostic or diagnostic for recurrence after primary, local therapy and for occurrence of occult distant micrometastasis in node-negative breast cancer. Elledge et al. analyze p53 status in node-negative, intermediate sized tumors and teach that additional prognostic factors in this group of tumors would aid in treatment decisions. Mutations in p53 exons were detected in DNA samples which were amplified by PCR followed by either SSCP or sequencing. Elledge et al. also teach that the exon location of the mutation affects the prognosis, with mutations in conserved exon 7 (which may be considered a biologically functional domain, region, or part) indicating a poorer prognosis. See the abstract; page 96, column 2, last two paragraphs; page 97; page 98, column 1, first full paragraph; page 100, column 1, first full

paragraph and last line on the page. Hartmann et al. (TIG, 13:p.28, 1997) show that exon 7 includes the DNA binding domain.

Elledge et al. do not teach the classification of neoplasia into different prognostic/diagnostic groups based on node status and p53 status.

Callahan teaches that lymph node status is the primary, art standard, parameter in prognosis of breast cancer and in guiding decisions with regard to adjunct therapy. Callahan teaches, however, that a percentage of node (-) patients relapse and that additional prognostic factors in these situations would be desirable. Callahan teaches, in this light, that p53 mutation is an independent prognostic marker and suggests the combination of nodal status and p53 status to distinguish patients who require aggressive postsurgical therapy. See the entire article.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to combine, with a reasonable expectation of success, the sequence-based p53 analysis of Elledge et al., including analysis of functional domains, including a DNA binding domain, with art standard nodal status assays, as taught by Callahan to prognostically classify neoplasia and one would have been motivated to do so in order to facilitate identification of patients in need of more aggressive postsurgical therapy as taught by Callahan.

7. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) as applied

above to claims 1-8 and further in view of Mitsudomi et al. (J. Nat. Cancer Inst. 85:2018-2023, 1993).

Elledge et al. and Callahan teach as set forth above but do not teach or suggest that the adjuvant therapy be radiation or chemotherapy/hormone therapy.

Mitsudomi et al. teach that impaired, i.e. mutated, p53 protein may have a high sensitivity to cytotoxic therapy such as chemotherapy and/or radiation therapy and suggest that such therapy would benefit p53 mutation-positive tumors. See page 2021, final two paragraphs.

Therefore, it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to use the method of Elledge et al. as modified by Callahan to provide guidance in selected adjuvant therapies of radiation or chemotherapy, with a reasonable expectation of success, because Mitsudomi et al. teach that p53 mutation-positive neoplasias would be expected to respond to such therapies.

8. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27:95-102, 1993) in view of Callahan (J. Natl.Cancer Institute. 84:826-827, 1992) and as evidenced by Hartmann et al. (TIG 13:28, 1997) as applied to claims 1-8 above and further in view of Hedrum et al. (BioTechniques, 17:118-129, 1993-IDS).

Elledge et al. and Callahan teach as set forth above but do not teach the use of automated, computer-aided or solid phase sequencing techniques.

Hedrum et al. teach the use of automated, robotic workstations in amplification and solid phase sequencing of p53 DNA to detect mutations for prognostic information. See the abstract; and page 118, column 3.

Therefore, it would have been *prima facie* obvious to and one of ordinary skill in the art would have been motivated to automate the assay of Elledge et al. as modified by Callahan., with a reasonable expectation of success as taught by Lindstrom and Hedrum et al. in order to streamline and analyze multiple samples for prognostic information.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Patent Examiner
June 5, 1998